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Cereal Grains: Humanity's Double-Edged Sword

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'Here is bread, which strengthens man's heart, and therefore called the sta of life'
(Mathew Henry: 1662–1714, Commentary on Psalm 104)
yet,
'Man cannot live on bread alone' (Bible, Matthew 4:4)

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Introduction

The number of plant species which nourish humanity is remarkably limited. Most of the 195,000 species of flowering plants produce edible parts which could be utilized by man; however less than 0.1% or fewer than 300 species are used for food. Approximately 17 plant species provide 90% of mankind's food supply, of which cereal grains supply far and away the greatest percentage (tables 1, 2). From table 1, it can be shown that the world's four major cereal grains (wheat, maize, rice and barley) contribute more tonnage

Table 1. The world's top 30 food crops (estimated edible dry matter)

		Million metric tons
1	Wheat	468
2	Maize	429
3	Rice	330
4	Barley	160
5	Soybean	88
6	Cane sugar	67
7	Sorghum	60
8	Potato	54
9	Oats	43
10	Cassava	41
11	Sweet potato	35
12	Beet sugar	34
13	Rye	29
14	Millets	26
15	Rapeseed	19
16	Bean	14
17	Peanut	13
18	Pea	12
19	Musa	11
20	Grape	11
21	Sunflower	9.7
22	Yams	6.3
23	Apple	5.5
24	Coconut	5.3
25	Cottonseed (oil)	4.8
26	Orange	4.4
27	Tomato	3.3
28	Cabbage	3.0
29	Onion	2.6
30	Mango	1.8

Adapted from Harlan [3].

to humanity's food supply than the next 26 crops combined. Eight cereal grains: wheat, maize, rice, barley, sorghum, oats, rye, and millet provide 56% of the food energy and 50% of the protein consumed on earth [1]. Three cereals: wheat, maize and rice together comprise at least 75% of the world's grain production (table 1). It is clear that humanity has become dependent upon cereal grains for the majority of its food supply. As Mangelsdorf [2] has pointed out, 'cereal grains literally stand between mankind and starvation'; therefore, it is essential that we fully understand the nutritional implications of cereal grain consumption upon human health and well being.

Modern man has become so dependent upon eating cereal grains (grass seeds) that it has prompted at least one author [3] to say that we have become 'canaries'. However, this has not always been the case. For the vast majority of mankind's presence on this planet, he rarely if ever consumed cereal grains [4]. With the exception of the last 10,000 years following the agricultural 'revolution', humans have existed as non-cereal-eating hunter-gatherers since the emergence of *Homo erectus* 1.7 million years ago. Although the first anatomically modern humans (*Homo sapiens*) appeared in Africa $>90{,}000$ years ago, humans prior to the mesolithic period (~15,000 years ago) like other primates rarely if ever utilized cereal grains [4]. Post-pleistocene (~10,000 years ago) hunter-gatherers occasionally consumed cereal grains; however these foods were apparently not major dietary components for most of the year [5]. It is apparent that there is little or no evolutionary precedent in our species for grass seed consumption [6–8]. Consequently, we have had little time (<500 generations) since the inception of the agricultural revolution 10,000 years ago to adapt to a food type which now represents humanity's major source of both calories and protein.

The sum of evidence indicates that the human genetic constitution has changed little in the past 40,000 years [7]. The foods which were commonly

Table 2. Food group totals (estimated edible dry matter)

		Million metric tons
1	Cereals	1,545
2	Tubers	136
3	Pulses	127
4	All meats, milk and eggs	119
5	Sugar	101
6	Fruits	34

Adapted from Harlan [3].

Table 3. Key events in the development of agriculture and domestication of cereal grains

Event	Time from present years	Location
Development of agriculture	10,000	Near East
	8,000	Greece, West Africa
	7–8,000	Central and S. America
	7,000	China, India and SE Asia
	6,500	Paris basin
	6,000	Central Africa
	5,500	Scandinavia, England
Domestication of wheat and barley	10,000	Near East
Domestication of rice	7,000	China, India and SE Asia
Domestication of maize	7,000	Central and S. America
Domestication of millets	5–6,000	Africa
Domestication of sorghum	5–6,000	East Africa
Domestication of rye	5,000	SW Asia
Domestication of oats	3,000	Europe

available to preagricultural man were the foods which shaped modern man's genetic nutritional requirements. Although our genetically determined nutritional needs have changed little in the past 40,000 years, our diet has changed dramatically since the advent of agriculture 10,000 years ago [7]. Cereal grains as a staple food are a relatively recent addition to the human diet (table 3) and represent a dramatic departure from those foods to which we are genetically adapted. Discordance between humanity's genetically determined dietary needs and his present day diet is responsible for many of the degenerative diseases which plague industrial man [9]. Although cereal grains are associated with virtually every highly developed civilization in mankind's history and now occupy the base of the present day food selection pyramid in the United States [10], there is a significant body of evidence which suggests that cereal grains are less than optimal foods for humans and that the human genetic makeup and physiology may not be fully adapted to high levels of cereal grain consumption.

Archaeological Perspective

At the close of the paleolithic era and during the mesolithic period (20,000–10,000 years ago), there was a widescale extinction of large mammals throughout Europe, North America and Asia [11] that coincided with a fundamental

change in how hunter-gatherer's made use of their environment and obtained their food sources. People all over the world began to adopt a broader spectrum of hunting and gathering which more fully utilized all niches in their environment. Tools and weapons became smaller, more elegant and more e cient [3]. The aquatic environment was increasingly exploited via boats, canoes, harpoons, fish nets, hooks and weirs. Birds and waterfowl began to appear more frequently in the fossil record associated with man's food supply. For the first time (15,000 years ago) grindstones and crude mortars appeared in the archaeological record in the near east [6], thereby heralding the beginnings of humanity's use of cereal grains for food. Since wild cereal grains are small, di cult to harvest and minimally digestible without processing (grinding) and cooking [5, 12, 13], the appearance of stone-processing tools is an essential indication of when and where cultures began to include cereal grains in their diet.

As human population numbers increased following the pleistocene (10,000 years ago) and as large grazing herbivores became either extinct or severely depleted, humanity became more and more reliant upon small mammals, fish, fowl and gathered plant foods to supply his caloric needs. Gradually, as these resources became depleted, in the face of increasing human population numbers, agriculture became the dominant way of life, and cereal grains became the dominant caloric and protein source in many, but not all prehistoric cultures [3, 14]. Whereas hunter-gatherers derived most of their calories from a diversity of wild animal meats, fruits and vegetables encompassing between 100 and 200 or more species [15], agricultural man became primarily dependent upon a few staple cereal foods, 3–5 domesticated meats and between 20 and 50 other plant foods. In many third-world countries and in a number of historical agrarian societies, a single cereal staple could provide up to 80% or more of the daily caloric intake with few or no calories regularly coming from animal sources [7, 16].

Generally, in most parts of the world, whenever cereal-based diets were first adopted as a staple food replacing the primarily animal-based diets of hunter-gatherers, there was a characteristic reduction in stature [4, 17–19], an increase in infant mortality [19, 20], a reduction in lifespan [19, 20], an increased incidence of infectious diseases [19–22], an increase in iron deficiency anemia [19, 20, 22], an increased incidence of osteomalacia, porotic hyperostosis and other bone mineral disorders [4, 19, 20, 22] and an increase in the number of dental caries and enamel defects [19, 20, 23]. In a review of 51 references examining human populations from around the earth and from di ering chronologies, as they made the transition from hunter-gatherers to farmers, Cohen [19] concluded that there was an overall decline in both the quality and quantity of life. There is now substantial empirical and clinical evidence to indicate that

many of these deleterious changes may be directly related to the predominantly cereal-based diet of these early farmers.

Cereal grains truly represent humanity's double-edged sword, for without them we likely would not have had an agricultural 'revolution'. We surely would not be able to sustain the enormous present-day human population (>6 billion), nor would there likely have been societal stratification which ultimately was responsible for the vast technological/industrial culture in which we live [21]. The enormous increase in human knowledge would probably never had taken place had it not been for the widespread adoption of agriculture by humanity, and our understanding of medicine, science and the universe is a direct outcome of the societal stratification wrought by the agricultural 'revolution' [21]. On the other hand, agriculture is generally agreed to be responsible for many of humanity's societal ills including whole-scale warfare, starvation, tyranny, epidemic diseases, and class divisions [21]. Cereals provide the major caloric and protein source for humanity and therefore are the mainstay of agriculture; they have allowed man's culture to grow and evolve so that man has become earth's dominant animal species, but this preeminence has not occurred without cost. Because of cereal grains mankind has dramatically altered his original culture; moreover cereal grains have fundamentally altered the foods to which our species had been originally adapted over eons of evolutionary experience. For better or for worse, we are no longer hunter-gatherers, however our genetic makeup is still that of a paleolithic hunter-gatherer, a species whose nutritional requirements are optimally adapted to wild meats, fruits and vegetables, not to cereal grains. We have wandered down a path toward absolute dependence upon cereal grains, a path for which there is no return. It is critical that we fully understand the nutritional shortcomings of cereal grains as we proceed.

Dietary Imbalances of Cereal Grains

All cereal grains have significant nutritional shortcomings which are apparent upon analysis. From table 4 it can be seen that cereal grains contain no vitamin A and except for yellow maize, no cereals contain its metabolic precursor, beta-carotene. Additionally, they contain no vitamin C, or vitamin B_{12}. In most western, industrialized countries, these vitamin shortcomings are generally of little or no consequence, since the average diet is not excessively dependent upon grains and usually is varied and contains meat (a good source of vitamin B_{12}), dairy products (a source of vitamins B_{12} and A), and fresh fruits and vegetables (a good source of vitamin C and beta-carotene).

Table 4. Vitamin and mineral content of eight unprocessed cereal grains (100-gram samples)

	Wheat	Maize	Rice	Barley	Sorghum	Oats	Rye	Millet
Vitamin								
B_1, mg	0.38	0.39	0.40	0.65	0.24	0.76	0.32	0.42
	(35%)	(35%)	(36%)	(59%)	(22%)	(69%)	(29%)	(38%)
B_2, mg	0.12	0.20	0.09	0.29	0.14	0.14	0.25	0.29
	(9%)	(15%)	(7%)	(22%)	(11%)	(11%)	(19%)	(22%)
B_3, mg	5.47	3.63	5.09	4.60	2.92	0.96	4.27	4.72
	(36%)	(24%)	(34%)	(31%)	(20%)	(6%)	(28%)	(31%)
B_6, mg	0.30	0.62	0.51	0.32	n.a.	0.12	0.29	0.38
	(21%)	(39%)	(32%)	(20%)	(n.a.)	(7%)	(18%)	(24%)
Folate, mg	38.2	19.0	19.5	19.0	n.a.	56.0	59.9	85.0
	(21%)	(11%)	(11%)	(11%)	(n.a.)	(31%)	(33%)	(47%)
Pantothenic acid, mg	0.95	0.42	1.49	0.28	n.a.	1.35	1.46	0.85
	(17%)	(8%)	(27%)	(5%)	(n.a.)	(24%)	(26%)	(15%)
Biotin	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	(n.a.)	(n.a.)	(n.a.)	(n.a.)	(n.a.)	(n.a.)	(n.a.)	(n.a.)
E, mg	n.a.	0.49	0.68	0.57	n.a.	1.09	1.28	0.05
	(n.a.)	(6%)	(9%)	(7%)	(n.a.)	(14%)	(16%)	(1%)
Mineral								
Potassium, mg	363	287	223	452	350	429	264	195
	(18%)	(14%)	(11%)	(23%)	(17%)	(21%)	(13%)	(10%)
Sodium, mg	2	35	7	12	6	2	6	5
	(0%)	(1%)	(0%)	(1%)	(0%)	(0%)	(0%)	(0%)
Calcium, mg	29.0	7.0	23.0	33.0	28.0	53.9	33.0	8.0
	(4%)	(1%)	(3%)	(4%)	(4%)	(7%)	(4%)	(1%)
Phosphorus, mg	288	210	333	264	287	523	374	285
	(36%)	(26%)	(42%)	(33%)	(36%)	(65%)	(47%)	(36%)
Magnesium, mg	126	127	143	133	n.a.	177	121	114
	(45%)	(45%)	(51%)	(48%)	(n.a.)	(63%)	(43%)	(41%)
Iron, mg	3.19	2.71	1.47	3.60	4.40	4.72	2.67	3.01
	(21%)	(18%)	(10%)	(24%)	(29%)	(31%)	(18%)	(20%)
Zinc, mg	2.65	2.21	2.02	2.77	n.a.	3.97	3.73	1.68
	(22%)	(18%)	(17%)	(23%)	(n.a.)	(33%)	(31%)	(14%)
Copper, mg	0.43	0.31	0.27	0.50	n.a.	0.63	0.45	0.75
	(19%)	(14%)	(12%)	(22%)	(n.a.)	(28%)	(20%)	(33%)
Manganese, mg	3.98	0.46	3.75	1.95	n.a.	4.92	2.68	1.63
	(114%)	(14%)	(107%)	(56%)	(n.a.)	(140%)	(77%)	(47%)
Selenium, mg	0.043	0.004	n.a.	0.066	n.a.	n.a.	n.a.	n.a.
	(78%)	(8%)	(n.a.)	(120%)	(n.a.)	(n.a.)	(n.a.)	(n.a.)

Values in (parentheses) represent RDA %. n.a. = Not available. No detectable amounts of vitamins A, C, D, B_{12} in any grain.

However, as more and more cereal grains are included in the diet, they tend to displace the calories that would be provided by other foods (meats, dairy products, fruits and vegetables), and can consequently disrupt adequate nutritional balance. In some countries of Southern Asia, Central America, the Far East and Africa cereal product consumption can comprise as much as 80% of the total caloric intake [16], and in at least half of the countries of the world, bread provides more than 50% of the total caloric intake [16]. In countries where cereal grains comprise the bulk of the dietary intake, vitamin, mineral and nutritional deficiencies are commonplace.

Vitamins A, C and Beta-Carotene

Vitamin A deficiency remains one of the major public health nutritional problems in the third world [24]. Twenty to 40 million children worldwide are estimated to have at least mild vitamin A deficiency [25]. Vitamin A deficiency is a leading cause of xerophthalmia and blindness among children and also a major determinant of childhood morbidity and mortality [26]. In virtually all infectious diseases, vitamin A deficiency is known to result in greater frequency, severity, or mortality [27]. A recent meta-analysis [28] from 20 randomized controlled trials of vitamin A supplementation in third world children has shown a 30–38% reduction in all cause mortality in vitamin A-supplemented children. Analysis of cause-specific mortality showed vitamin A supplementation elicited a reduction in deaths from diarrheal disease by 39%, from respiratory disease by 70% and from all other causes of death by 34% [28]. Clearly, the displacement of beta-carotene-containing fruits and vegetables and vitamin A-containing foods (milk fat, egg yolks and organ meats) by excessive consumption of cereal grains plays a major role in the etiology of vitamin A deficiency in third world children.

In numerous epidemiologic studies, an increased intake of fruits and vegetables has been associated with a reduced risk of many types of cancer [29, 30] and coronary heart disease (CHD) [31, 32]. Much of the evidence for the link between fruit, vegetables and cancer and CHD points to those foods rich in antioxidants, including vitamin C, carotenoids and phytochemicals. In the United States, an estimated 45% of the population had no servings of fruit or juice, and 22% had no servings of a vegetable on any given day [33]. Further, 91% of the adult population did not meet the United States Department of Agriculture's daily recommendation of 2–3 servings of fruit and 3–5 servings of vegetables [33]. Although frank vitamin C deficiency is virtually unknown in the United States and other western countries, it has been shown to be common in portions of rural India wherein cereals and pulses comprise the dietary mainstays, and vitamin C-rich fruits and vegetables are consumed in low quantities [34]. Again, since cereal grains contain unde-

tectable amounts of vitamin C and carotenoids, they tend to displace foods rich in these substances; foods which are associated with a decreased risk for many common cancers [35] and heart disease [31, 32].

Cereal- and pulse-based diets of the third world generally tend to be considerably lower in both total fat, saturated fat and cholesterol than the meat-based diets of western countries [36], yet paradoxically, CHD mortality is in some cases either higher [36] or similar [36, 37] to that in western countries. Since the antioxidant status of CHD-prone individuals chronically consuming cereal- and pulse-based diets has been shown to be low [36, 38], and increased consumption of fruit and vegetables has been shown to improve the CHD risk profile of this population [39], it is likely that high cereal grain consumption partially contributes to increased CHD mortality via its displacement of antioxidant rich fruits and vegetables.

B Vitamins

Diets based primarily or wholly upon plant food sources tend to be either low or deficient in vitamin B_{12}, since this nutrient is found exclusively in animal products [40]. Vitamin B_{12} deficiency causes a megaloblastic anemia which ultimately results in cognitive dysfunction via its irreversible impact on the neurological system [41]. Additionally, it is known that a chronic B_{12} deficiency produces elevated homocysteine levels [42, 43] which are an important risk factor for arterial vascular disease and thrombosis [43, 44]. Vitamin B_{12} deficiency is generally assumed to be uncommon because omnivorous diets provide adequate intake, and the vitamin is conserved e ciently by the enterohepatic circulation [40]. However, in countries such as India in which the diets are mainly cereal and pulse based, vitamin B_{12} deficiencies are common [45, 46]. Additionally, even if minimal amounts of animal-based foods are consumed along with traditional cereal- and pulse-based diets, intestinal infection, which is widespread in the third world, has been shown to worsen an already compromised B_{12} status and result in widespread B_{12} deficiencies [47]. The human nutritional requirement for vitamin B_{12} clearly demonstrates that vegetarian diets based entirely upon cereal grains, legumes and other plant foods were not the sole dietary components which shaped the human genome.

Many nutritionists consider cereal grains to be good sources of most of the B vitamins except for vitamin B_{12}. Inspection of table 4 generally is supportive of this concept, at least in terms of the % RDA which cereal grains contain. However, of more importance is the biological availability of the B vitamins contained within cereal grains and their B vitamin content after milling, processing and cooking. It is somewhat ironic that two of the major B vitamin deficiency diseases which have plagued agricultural man (pellagra and beriberi) are almost exclusively associated with excessive consumption of cereal grains.

Beriberi occurs from a thiamin deficiency which is associated with polished rice consumption. In the late 1800s, with the introduction of polished rice, beriberi reached epidemic proportions in Japan and other countries in Southeast Asia [48]. Human crossover experiments done in the early part of this century induced beriberi in subjects fed polished rice, but not in those fed brown rice [48]. The removal of the outer thiamin-containing coat of the rice kernel during the polishing process was found to be the factor responsible for inducing beriberi in rice-eating populations [48]. Beriberi has been largely eliminated with the advent of 'enriched rice' to which thiamin is added, but still occurs in some African countries whose populations consume high quantities of polished rice [49].

Pellagra is thought to be a multiple deficiency disease caused by a lack of niacin and the essential amino acid tryptophan [14], and occurs almost exclusively in people eating corn as their staple food. In the United States between 1906 and 1940 there was an epidemic of pellagra in the southern states which resulted in approximately 3 million cases with at least 100,000 deaths [50]. Similar epidemics have occurred in Europe and India [51], and pellagra is still widespread in parts of Africa [52, 53]. Although administration of niacin is known to rapidly eliminate all symptoms of pellagra, there is a continuing suspicion that not all of the precipitating factors which operate in maize to elicit overt symptoms of pellagra are understood [54, 55]. Traditional lime-processing techniques of corn (boiling of dried corn flour for 30–50 min in a 5% lime water solution) prevents pellagra, and it is thought to do so by increasing niacin's availability [14]. However, a modern study [55] recently reanalyzed historical pellagra-inducing diets and even after correcting for niacin's low availability, found these diets to be adequate in niacin equivalents (niacin + 0.0166 × tryptophan), suggesting that factors in corn other than low niacin and tryptophan were responsible for the disease. Corn, like all cereal grains, is rich in antinutrients including lectins which are known to decrease intestinal absorption of many key nutrients [56, 57]. Since villous atrophy of the small intestine has been demonstrated in patients with pellagra [58], it is possible that certain antinutrients in maize could interfere with intestinal absorption of both niacin and tryptophan or that plasma-borne antinutrients could interfere with the conversion of tryptophan to niacin similar to the e ects of isoniazid, an anti-tuberculous drug which is known to produce pellagra-like symptoms [59].

Although table 4 suggests that most cereal grains except for oats are relatively good sources of vitamin B_6, the bioavailability of B_6 from cereal grains tends to be low, whereas bioavailability of B_6 from animal products is generally quite high, approaching 100% [60]. Vitamin B_6 exists in foods as three nonphosphorylated forms (pyridoxine, pyridoxal and pyridoxamine) and two phosphorylated forms of pyridoxal and pyridoxamine. An additional

glycosylated adduct of pyridoxine, pyridoxine glucoside, occurs widely in cereal grains and has been shown to reduce the bioavailability of both nonphosphorylated and phosphorylated forms of vitamin B_6 by 75–80% [60, 61]. The presence of pyridoxine glucoside in cereal grains has an overall e ect of depressing the vitamin B_6 nutritional status [62]. Data from Nepalese vegetarian lactating women has shown a low vitamin B_6 status for both the mothers and their infants which was partially attributed to the high levels of pyridoxine glucosides found in their cereal-, legume- and plant-based diet [60]. B_6 deficiencies appear to be quite common in populations utilizing cereals and pulses as staples [63, 64]. Low tissue levels of vitamin B_6, like vitamin B_{12} are known to elevate plasma homocysteine levels and increase the risk for arterial vascular disease [43]. To date, plasma homocysteine levels have not been evaluated in cereal- and pulse-eating populations of the Indian subcontinent wherein there is a high mortality rate from CHD [36].

Perhaps the least studied of the B complex vitamins is biotin. Animal studies have shown that most cereal grains except maize have very low levels of bioavailable biotin [65, 66], whereas foods derived from animal sources have a high biotin digestibility [66]. Both wheat and sorghum not only have a low biotin bioavailability, but seem to have elements within them which seem to elicit a depression of biotin metabolism [66]. The enzyme, biotinidase, recycles the biotin derived from the turnover of the biotin-dependent carboxylases and from exogenous protein-bound dietary biotin (fig. 1). Whether or not antinutrients present in cereal grains interfere with biotinidase is not known. However, the biotin-dependent carboxylases are important metabolic pathways of fatty acid synthesis. A biotin deficiency severely inhibits the chain elongation and desaturation of linoleic acid to arachidonic acid [67] (fig. 2), and biotin-deficient rats are known to exhibit prominent cutaneous symptoms including scaling, seborrheic dermatitis and alopecia [68], symptoms which are identical in humans with biotin and biotinidase deficiencies. Recent human biotin supplementation trials have shown this vitamin to reduce fingernail brittleness [69]. Anecdotal evidence has suggested that subjects who had adopted the Pritikin diet (a low-fat diet based primarily upon cereal grains) for periods of 1–2 years developed vertical ridges on their fingernails [70]. It is unclear if these symptoms are caused by impaired biotin metabolism; however the available research on this poorly studied vitamin suggests that diets based primarily upon cereal grains are responsible for causing biotin deficiencies in a variety of laboratory animals.

Minerals

Table 4 displays the mineral content and the percent of the recommended daily allowance (RDA) in a 100-gram sample of the world's most commonly

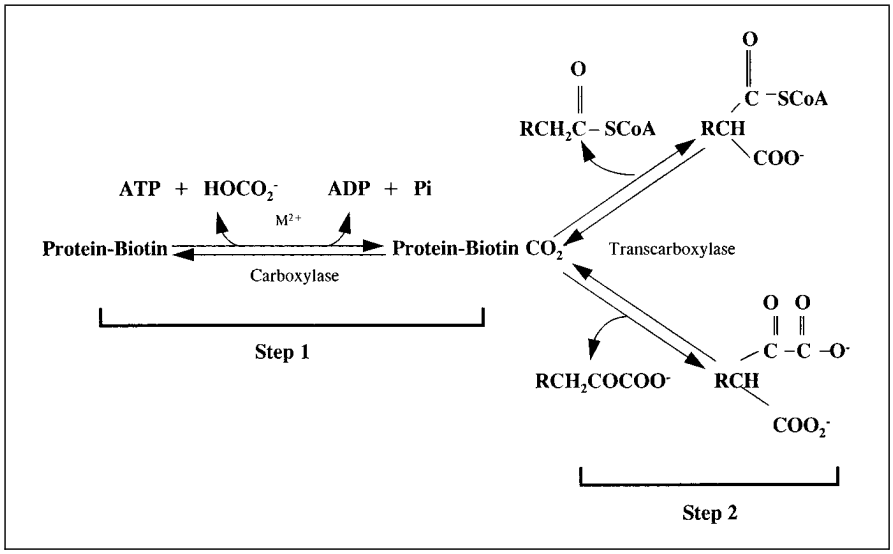

Fig. 1. Biotin metabolism. Biotin-dependent carboxylation reactions can be divided into step 1 (the formation of carboxyl biotinyl enzyme), and step 2 (carboxyl transfer to an appropriate acceptor substrate, dependent upon the specific transcarboxylase involved).

consumed cereal grains. Of the minerals, cereal grains are poor sources of sodium and calcium but are relatively rich sources of phosphorous, potassium and magnesium. Not all of the minerals are included in table 4; however it can be seen that cereal grains contain moderate amounts (10–33%) of zinc, copper and iron and high amounts of manganese.

Calcium. Except for calcium and sodium, it would appear that cereal grains provide reasonable amounts of most minerals needed for adequate nutrition. Since the western diet is already overburdened by high dietary sodium levels [71], the low sodium content of cereal grains is desirable. In most western populations that consume a mixed diet, the low calcium content of cereal grains does not normally represent a problem since dairy products and leafy green vegetables are good sources of calcium, if they are included in the diet. However, as is the case for vitamins, as more and more cereal grains are included in the diet, they tend to displace dairy and vegetable sources of calcium. Further, cereal grains have a Ca/P ratio which is quite low (mean from table 4 = 0.08) and which can negatively impact bone growth and metabolism. Consumption of a large excess of dietary phosphorus, when calcium intake is adequate or low, leads to secondary hyperparathyroidism and progressive bone loss [72]. The recommended, ideal Ca/P ratio is 1:1,

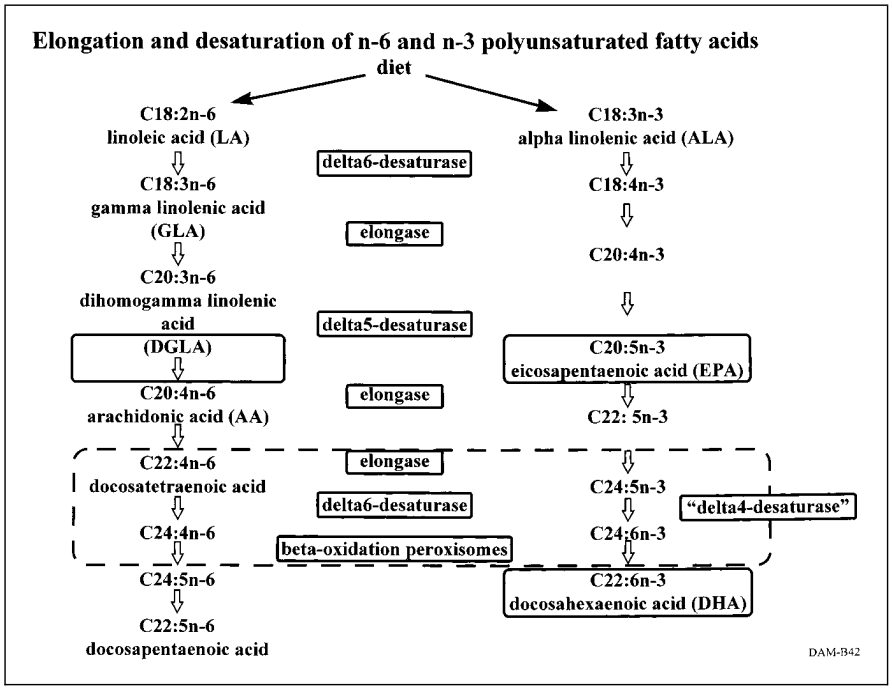

Fig. 2. The essential fatty acids and their long-chain polyunsaturated metabolites.

whereas in the United States it averages 0.64 for women and 0.62 for men [72]. In addition to the unfavorable Ca/P ratio, cereal grains maintain a quite low Ca/Mg ratio (averaging 0.19 from table 4) which also favors net Ca excretion, since imbalances in Mg intake relative to Ca decrease gastrointestinal absorption and retention of Ca [73, 74]. Because of the high phytate content of whole grain cereals much of the calcium present is unavailable for absorption because the phytate forms insoluble complexes with calcium [75]. The net e ect of a low calcium content, a low Ca/P ratio, a low Ca/Mg ratio, and low bioavailability of calcium via a high phytate content frequently induces bone mineral pathologies in populations dependent upon cereal grains as a staple food. In populations where cereal grains provide the major source of calories, osteomalacia, rickets and osteoporosis are commonplace [76–79]. Cereal grains have been shown to cause their rachitogenic- and osteomalacia-producing e ects in spite of the presence of adequate sunshine [80]. Further, substitution of leavened white breads of lower extraction for unleavened whole grain breads improved biochemical symptoms in patients with rickets or osteomalacia [77].

Consumption of high levels of whole grain cereal products impairs bone metabolism not only by limiting calcium intake, but by indirectly altering vitamin D metabolism. In animal studies it has been long recognized that excessive consumption of cereal grains can induce vitamin D deficiencies in a wide variety of animals [81–83] including primates [84]. Epidemiological studies of populations consuming high levels of unleavened whole grain breads show vitamin D deficiency to be widespread [85–87]. A study of radiolabelled 25-hydroxyvitamin D_3 ($25(OH)D_3$) in humans consuming 60 g of wheat bran daily for 30 days clearly demonstrated an enhanced elimination of $25(OH)D_3$ in the intestinal lumen [88]. The mechanism by which cereal grain consumption influences vitamin D is unclear. Some investigators have suggested that cereal grains may interfere with the enterohepatic circulation of vitamin D or its metabolites [84, 88], whereas others have shown that calcium deficiency increases the rate of inactivation of vitamin D in the liver [89]. This e ect is mediated by 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) produced in response to secondary hyperparathyroidism, which promotes hepatic conversion of vitamin D to polar inactivation products which are excreted in bile [89]. Consequently, the low Ca/P ratio of cereal grains has the ability to elevate PTH which in turn stimulates increased production of $1,25(OH)_2D$ which causes an accelerated loss of 25-hydroxyvitamin D.

Iron. In addition to their deleterious influence upon calcium metabolism, cereal grains when consumed in excessive quantities can adversely influence iron metabolism. Because of their fiber and phytate content, the bioavailability of iron in cereal grains is quite low [75, 90]. Iron deficiency is the most prevalent nutritional problem in the world today a ecting 2.15 billion people throughout the world and being severe enough to cause anemia in 1.2 billion people [91, 92]. The causative factor has been clearly demonstrated to be the poor bioavailability of iron from cereal-based diets, which are the staple food in many developing countries [93]. The displacement of iron-rich animal foods by cereal grains, legumes and plant-based diets is thus largely indirectly responsible for the worldwide epidemic of iron deficiency. Iron deficiency is known to reduce work capacity and productivity in adults, increase the severity and incidence of infection, and increase maternal, prenatal and perinatal mortality [94]. Perhaps the most serious e ect of iron deficiency is the often irreversible impairment of a child's learning ability [94].

There appear to be a number of elements within cereal grains which may inhibit nonheme iron absorption including phytate [75], tannins [95], fiber [75], lectins [96], phosphate [97] and perhaps other unknown factors [98]. However, the primary inhibitor of nonheme iron absorption by cereal grains is its phytate content [98]. Recent work has indicated that phytate must be almost totally removed to eliminate its inhibitory e ect on nonheme iron absorption [99].

Consequently, diets based upon whole grain maize [100], rice [101], wheat [102] and oats [103] have been consistently shown to reduce iron absorption. Nonheme iron absorption can be enhanced by including ascorbate-rich fruit and vegetables with cereal-based meals [101]. Further, the addition of yeast fermentation to make leavened breads is known to reduce their phytate content [102]. Additionally, fortification of cereal grains with iron has been shown to be an e ective procedure to prevent iron deficiency anemia [104, 105].

Other Minerals. In addition to calcium and iron, the bioavailability of zinc, copper and magnesium in cereal grains is generally low [75], whereas the absorption of manganese, chromium and selenium does not appear to be impaired [90]. Except for zinc, the clinical implications of deficiencies in these minerals relative to cereal grain consumption have been poorly studied. Consequently, few links have been established between high cereal grain consumption and deficiencies of copper, magnesium, manganese, chromium and selenium in human diets. However, there is substantial evidence which demonstrates that relatively high consumption of cereal grains can have a detrimental influence upon zinc metabolism and thus adversely a ect human health and well-being.

Zinc. Radiolabelled studies of zinc absorption in rats [106] and humans [107] have clearly demonstrated that consumption of whole grain cereals (wheat, rye, barley, oats and triticale) impairs zinc absorption. Similar to iron, it appears that phytate plays a major role in the inhibition of zinc absorption [106, 107]; however, other factors are likely involved [106]. In humans, zinc deficiency results in a characteristic syndrome called hypogonadal dwarfism in which there is arrested growth, hypogonadism and delayed onset of puberty [108]. In rural Iran where unleavened, whole grain flat bread (tanok) contributes at least 50% of the daily calories [106], the incidence of hypogonadal dwarfism was estimated to be nearly 3% in 19-year-old conscripts [109]. Since the zinc intake of these populations exceeds the RDA by a substantial margin [109], it has been shown that the high consumption of tanok is responsible for inducing negative zinc balances [110]. Recent studies of nonhuman primates moderately deprived of zinc [111] as well as zinc supplementation trials in children [112] have confirmed Reinhold's earlier work [109] showing how marginal zinc nutriture, independent of other nutrients, may limit skeletal growth. Yeast leavening of whole grain breads can reduce their phytate content and improve the bioavailability of zinc [106]; however increased ascorbic acid intake does not enhance the absorption of zinc [103]. Because the bioavailability of zinc from meat is four times greater than that from cereals [113], it is clear that the displacement of animal-based foods by cereal-grain- and plant-based diets is not only responsible for impaired zinc metabolism in developing countries, but also in western populations adopting vegetarian diets [114, 115].

Essential Fatty Acids

Cereal grains are quite low in fats (table 6) averaging 3.6% fat for their total caloric content; even still a predominantly cereal- and plant-based diet can contribute 5–10 g per person per day of linoleic acid (LA), the major Ω-6 (n-6) polyunsatuarated fatty acid found in grains [5]. The linolenic acid content of cereals is quite low, and they are devoid of the longer chain Ω-3 (n-3) derivatives of linolenic acid, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Consequently, cereal-based diets, particularly if they are supplemented by vegetable oils, tend to have a high n-6/n-3 ratio (table 6) and are deficient in EPA, DHA and long-chain derivatives of LA including arachidonic acid (AA).

In man, the longer chain fatty acids can be synthesized from their shorter chain precursors; however the process is ine cient [117], and because linoleic and linolenic acid must utilize the same desaturase and elongase enzymes, there is competitive inhibition of one another, so that high dietary levels of linoleic acid tends to inhibit the formation of EPA from linolenic acid if preformed EPA is not obtained directly in the diet from fish or meat sources. The importance of certain long-chain fatty acids [20:3n-6 (dihomogammalinolenic acid), 20:4n-6 (AA) and 20:5n-3 (EPA)] is that they serve as precursors for the synthesis of eicosanoids (the prostaglandins, prostacyclins, thromboxanes, and leukotrienes), potent hormone-like substances which have a variety of e ects including regulation of platelet aggregation, thrombosis and inflammation [118]. Increased dietary consumption of n-3 fatty acids, particularly EPA has been shown to decrease triglycerides, decrease thrombotic tendencies [119] and reduce symptoms of many inflammatory and autoimmune diseases including arthritis [120] and inflammatory bowel disease [121]. Additionally, epidemiological studies indicate a reduced mortality from coronary heart disease in populations consuming increased amounts of n-3 fatty acids [122].

Vegetarian diets based primarily upon cereals, legumes and plant products are known to have a high n-6/n-3 ratio because of their low levels of both linolenic acid and the absence of its long-chain derivatives, EPA and DHA [123]. Studies of preterm infants deprived of DHA have shown both visual and cortical abnormalities [124]. A recent study of South Asian vegetarian mothers has indicated lower plasma levels of EPA and DHA when compared to white nonvegetarians [125]. Additionally, cord DHA levels were lower in the vegetarian mothers, and the duration of gestation was 5.6 days shorter than the meat-eating controls. In the vegetarian women early onset of labor and emergency cesarean section were more common, and birth weight, head circumference and body length were lower in the infants born to the vegetarian women [125].

In the United States, the US Department of Agriculture has recently adopted a 'food pyramid' of nutritional recommendations that places grains and pasta at the bottom (i.e. to be eaten in the largest amounts; 6–11 servings per day). It has recently been argued that a diet of this nature likely encourages essential fatty acid (EFA) deficiencies and may lead to an increased incidence of atherosclerosis [126]. The recommendation for a low-fat/high-carbohydrate diet, which is high in trans fatty acids due to margarine intake, leads to decreases in EFA. Since the standard American diet falls considerably short of the 6–11 servings of cereal grains recommended by the USDA [127], it is unlikely that cereal grain consumption, by itself, adversely influences the EFA status of the average American omnivorous diet. However, there are world populations in which excessive cereal grain consumption clearly has a deleterious impact upon essential fatty acid status. Studies of vegetarian and nonvegetarian populations from the Indian subcontinent who derive the bulk of their caloric intake from cereals and pulses have consistently demonstrated high plasma n-6/n-3 ratios, low levels of 20:5n-3 and 22:6n-3 and high levels of 18:2n6 when compared to western populations [125, 128–130]. Associated with these altered fatty acid levels is a mortality rate from CHD which is equal to [36, 37] or higher than [36, 129, 130] that found in western populations. Although the precise etiology of high levels of CHD in Indian populations is unclear, reduced plasma levels of n-3 fatty acids likely increase the risk for CHD by a variety of mechanisms which influence blood lipids, blood pressure, blood thrombic tendencies, and cardiac arrhythmias [119]. Since the western diet is already overburdened by an excessively high (n-6/n-3) ratio from vegetable oils, margarine and shortening [131], nutritional recommendations encouraging increased cereal grain consumption at the expense of fruits, vegetables, seafood and lean meats may indirectly contribute to an EFA profile which promotes CHD.

There is substantial evidence to show that low-density lipoprotein (LDL) oxidation plays an integral role in atherogenesis [132], and that diets enriched in linoleic acid increase the linoleic acid content of LDL and therefore increase its susceptibility to oxidation [133]. Blankenhorn et al. [134] have found that increased intake of linoleic acid significantly increased the risk of developing new atherosclerotic lesions in human coronary arteries. Further, the linoleic acid content of adipose tissue has been positively associated with the degree of CHD in patients undergoing coronary angiography [135]. Because cereal-grain- and pulse-based diets are quite high in linoleic acid (table 6), populations consuming these diets have been shown to have elevated plasma levels of linoleic acid when compared to western populations [125, 129]. It is possible that the high mortality rates of these populations [36, 129, 130] may be partially attributable to a high linoleic acid intake which increases the oxidative susceptibility of LDL.

These facts underscore the importance of a proper dietary balance of not only the short-chain n-3 and n-6 fatty acids, but of the preformed long-chain fatty acids of both the n-3 and n-6 families which are only found in foods of animal and marine origin. A diet based primarily upon cereal grains, legumes and plant foods inevitably leads to a disruption of this delicate balance among the dietary fatty acids, and ultimately may alter optimal health via subtle changes in eicosanoid, prostaglandin, prostacyclin, thromboxane and leukotriene function in various tissues. Human dietary lipid requirements were shaped eons ago, long before the agricultural revolution, and long before humanity's adoption of cereal grains as staple foods. Hence, the lipid composition of diets based upon cereal grains, legumes, vegetable oils and other plant products is vastly at odds with that found in wild game meat and organs [6], the primary, evolutionary source of lipids to which the human genetic constitution is optimally adapted [5].

Amino Acids

Because human body proteins constantly undergo breakdown and resynthesis during growth, development and aging, there is a dietary need for protein. Human body proteins are composed of 21 separate amino acids which are divided into three categories: (1) essential; (2) conditionally essential, and (3) nonessential. The nine essential amino acids cannot be synthesized in the body and consequently must be supplied by diet. The conditionally essential amino acids can be endogenously synthesized, however under certain physiological and pathological conditions, endogenous synthesis is inadequate and needs must be met by the diet. The nonessential amino acids can be endogenously synthesized under all conditions if there is an adequate dietary source of usable nitrogen. Consequently, in order for normal human protein metabolism to take place, there must be an adequate dietary intake (qualitative) of all 9 essential amino acids as well as an adequate intake (quantitative) of protein for synthesis of the conditionally essential and nonessential amino acids. The long-term metabolic consequences of imbalanced or marginally insu cient dietary amino acid intake in humans are not well documented; however there is evidence which suggests these types of diets can result in impaired linear growth [136], losses of body mass, muscular strength and impaired immune function [137] as well as impaired recovery from illness [138] and surgery [139].

Table 7 contrasts the amino acid contents of animal food sources to that in cereal grains and legumes. Inspection of both tables 5 and 7 show that the essential amino acid, lysine, is consistently lower in cereal proteins compared to animal proteins. Also, the essential amino acid, threonine, tends to be lower in cereal-based proteins relative to animal protein sources. The relative protein

Table 5. Amino acid and nutrient composition of eight unprocessed cereal grains (100-gram samples)

	Wheat	Maize	Rice	Barley	Sorghum	Oats	Rye	Millet
Essential amino acids								
Tryptophan, mg	160	67	101	208	124	234	154	119
	(64%)	(27%)	(40%)	(83%)	(50%)	(94%)	(62%)	(48%)
Threonine, mg	366	354	291	424	345	575	532	354
	(81%)	(79%)	(65%)	(94%)	(77%)	(128%)	(118%)	(79%)
Isoleucine, mg	458	337	336	456	433	694	550	465
	(71%)	(52%)	(52%)	(70%)	(67%)	(107%)	(85%)	(72%)
Leucine, mg	854	1,155	657	848	1,491	1,284	980	1,400
	(90%)	(122%)	(69%)	(89%)	(157%)	(135%)	(103%)	(147%)
Lysine, mg	335	265	303	465	229	701	605	212
	(42%)	(33%)	(38%)	(58%)	(29%)	(88%)	(76%)	(26%)
Methionine, mg	201	198	179	240	169	312	248	221
	(47%)	(46%)	(42%)	(56%)	(40%)	(73%)	(58%)	(52%)
Cystine*, mg	322	170	96	276	127	408	329	212
	(76%)	(40%)	(23%)	(65%)	(30%)	(96%)	(77%)	(50%)
Phenylaline, mg	593	463	410	700	546	894	673	580
	(125%)	(97%)	(86%)	(147%)	(115%)	(188%)	(142%)	(122%)
Tyrosine*, mg	387	383	298	358	321	573	339	340
	(81%)	(81%)	(63%)	(75%)	(68%)	(121%)	(71%)	(72%)
Valine, mg	556	477	466	612	561	937	747	578
	(85%)	(73%)	(72%)	(94%)	(86%)	(144%)	(115%)	(89%)
Histidine, mg	285	287	202	281	246	405	367	236
	(52%)	(52%)	(37%)	(51%)	(45%)	(74%)	(67%)	(43%)
Nutrient composition								
Kilocalories	327	365	370	354	339	389	335	378
Protein, % total calories	12.6	9.4	7.9	12.5	11.3	16.9	14.7	11.0
Carbohydrate, % total calories	71.3	74.1	77.2	73.3	74.4	66.0	69.8	73.0
Fat, % total calories	1.5	4.7	2.9	2.3	3.3	6.9	2.5	4.2

Values in (parentheses) represent RDA %. No detectable amounts of taurine in any grain.
* Conditionally essential amino acids.

content of cereal grains averages 12.0% (table 5) whereas that in lean beef is 22%. Consequently, a higher total intake of cereal products would be required to meet the needs for both total protein and certain individual essential amino acids when compared to animal foods.

Table 8 clearly indicates that cereal grains provide the majority of protein calories for most countries of the world. Because cereal-based diets frequently

Table 6. Fatty acid content of cereal grains (g fatty acid/100-gram sample): adapted from Weihrauch et al. [116]

Fatty acid	Wheat	Maize	Rice	Barley	Sorghum	Oats	Rye	Millet
Saturated fats								
14:0 (myristic acid)	–	0.00	0.03	0.01	0.01	0.02	–	0.00
16:0 (palmitic acid)	0.36	0.40	0.54	0.45	0.44	1.21	0.25	0.68
18:0 (stearic acid)	0.01	0.06	0.04	0.02	0.03	0.10	0.02	0.16
20:0 (arachidic)	–	0.01	0.01	0.00	0.00	0.04	0.00	0.02
Monounsaturated fats								
16:1 (palmitoleic)	0.01	0.01	0.01	0.01	0.04	0.02	0.01	0.02
18:1 (oleic acid)	0.25	0.91	0.54	0.24	1.15	2.60	0.22	0.83
Polyunsaturated fats								
18:2n-6 (linoleic acid)	1.20	2.12	0.78	1.14	1.46	2.87	0.95	1.69
18:3n-3 (linolenic acid)	0.10	0.03	0.03	0.13	0.09	0.16	0.12	0.13
Ratio (n-6/n-3)	12.0	70.7	26.0	8.7	16.2	17.9	7.9	13.0
Fat, % total calories	2.7	4.1	2.3	2.8	3.3	7.4	2.2	4.1

– = < 0.005 g.

include legumes and small amounts of animal protein, they are almost always adequate in the qualitative aspect of amino acid nutriture [140]; however the possibility exists that lysine intake may be marginal [140], particularly in children receiving a single or limited number of food protein choices [141].

Although cereal- and legume-based diets are usually adequate in the qualitative aspects of amino acid nutriture, there is evidence that under some circumstances they may fall short in quantitative aspects. The current estimated mean dietary protein requirements for healthy adult men and women of all ages is 0.6 g/kg/day, with a suggested safe protein intake set at 0.75 g/kg/day by the Joint FAO/WHO/UNU Expert Consultation [142] and at 0.8 g/kg/day by the Food and Nutrition Board of the US National Research Council [143]. There is now considerable evidence to suggest that these recommendations are too low for both adults [144, 145] and the elderly [146] and that safe

Table 7. Amino acid distribution in cereal, legume and animal food sources: adapted from Young et al. [140]

Food	Lysine content mg/g protein	Sulfur amino acids mg/g protein	Threonine mg/g protein	Tryptophan mg/g protein
Cereal grains	31 ± 10	37 ± 5	32 ± 4	12 ± 2
Legumes	64 ± 10	25 ± 3	38 ± 3	12 ± 4
Animal foods	85 ± 9	38	44	12

Table 8. Nutritional contributions of cereal grains to various regions of the world: adapted from Young et al. [141]

Region	Caloric intake g	Caloric intake from cereals %	Protein intake g	Protein intake from cereals %
North America	3,557	17	105.7	18
Western Europe	3,376	26	94.8	29
Eastern Europe and USSR	3,481	38	103.3	37
Latin America	2,557	39	65.5	38
Africa	2,205	47	55.0	51
Near East	2,620	61	73.5	62
Far East	2,029	67	48.7	63
All developed countries	3,395	31	99.1	30
All developing countries	2,260	61	57.3	55
World	2,571	50	68.8	45

dietary protein intakes may be as high as 1.0–1.25 g/kg/day [145, 146]. The elderly are particularly vulnerable to inadequate protein intakes. A nutritional survey of 946 free-living men and women in the United States over the age of 60 years showed that approximately half of them consumed less than 1.0–1.25 g/kg/day of protein [147]. Because the total protein content of cereal grains is considerably less than that in animal-based foods (table 7), the displacement of animal foods by excessive consumption of cereal grains has the potential to compromise adequate protein intake. Indeed, only 2 of 8 elderly Brazilian men consuming their typical rice and bean diet (containing 0.63 g/kg/day protein) were able to achieve positive nitrogen balance [148]. Because cereal-grain-based diets provide at least 50% of the protein calories for the world population, it is quite likely that inadequate protein intake in the elderly may be quite common [137, 146, 148].

Although taurine is considered a conditionally essential amino acid, there is increasing recognition that humans have limited ability to synthesize taurine

Table 9. Diseases which may occur simultaneously with celiac disease

Addison's disease
Aphthous ulceration
Asthma
Atopic diseases
Autoimmune thyroid diseases
Dental enamel defects
Dermatitis herpetiformis
Epilepsy with cerebral calcifications
Insulin-dependent diabetes mellitus
IgA nephropathy
Liver disease
Chronic active hepatitis
Primary sclerosing cholangitis
Primary biliary cirrhosis
Rheumatoid arthritis
Selective IgA deficiency
Sjogren's syndrome
Systemic lupus erythematosus

from cysteine [149, 150], consequently dietary taurine plays an important role in maintaining body taurine pools [151, 152]. All plant foods have undetectable amounts of taurine [153] including cereal grains (table 5). Studies of vegans have shown them to maintain lower levels of both plasma and urinary taurine [154, 155]. The clinical sequelae of long-term taurine deficiency in individuals consuming cereal- and plant-based diets has not been studied. However, taurine is known to positively influence cardiovascular disease by reducing platelet aggregation [156], by reducing reperfusion injury via free radical scavenging action [157], and by exhibiting antiarrhythmic activity [158]. Furthermore, taurine appears to have an essential role in the posttrauma state [159, 160] and in maintaining normal retinal function [161].

Consistent with populations from the fossil record showing a characteristic reduction in stature with the adoption of cereal-based agriculture [4, 17–19], is the observation that present-day populations depending upon cereal grains for the bulk of their energy and protein also tend to be of short stature [162–165]. Further, vegan and vegetarian children often fail to grow as well as their omnivorous cohorts despite apparently adequate intakes of amino acids and nitrogen [166]. There are a variety of reasons why cereal-based diets may impair linear growth. These include deficiencies in energy, protein, zinc, iron, copper, calcium, vitamin D, vitamin B_{12} and vitamin A [136, 166]. However, for none of these nutrients is there clear, consistent evidence that supplementation with the nutrient benefits linear growth [136]. It is likely that

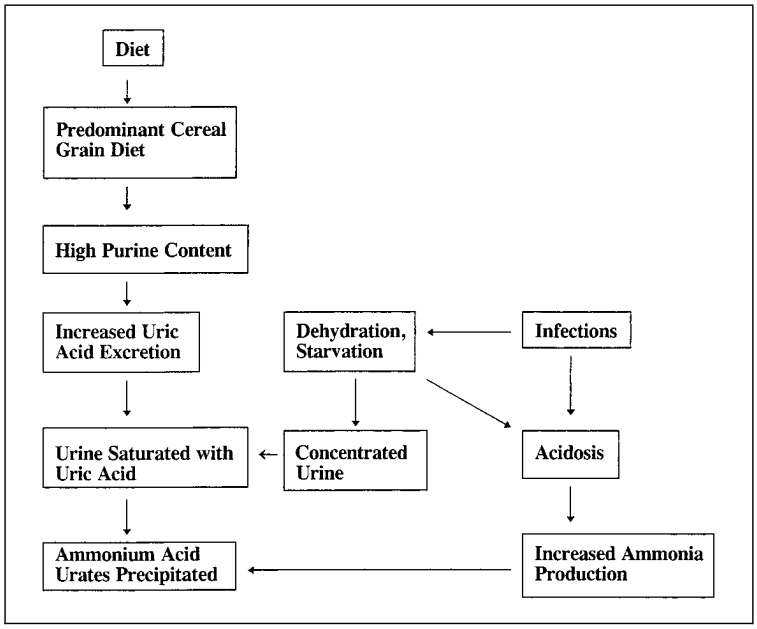

Fig. 3. Pathogenesis of childhood urinary bladder stones. Adapted from Teotia et al. [174].

growth and hence adult stature is limited by multiple, simultaneous deficiencies [136] in populations dependent upon cereal grains for the bulk of their caloric intake. Excessive consumption of cereal grains clearly has a deleterious e ect upon virtually all of the previously listed nutrients.

Childhood urinary bladder stones have virtually disappeared from western countries, however they are still very common in developing countries such as Pakistan, India, Thailand, Sumatra, Taiwan and Iran [167–170]. These stones are composed primarily of ammonium acid urate, and studies of children in these areas have demonstrated increased urinary excretion of oxalate ammonia and uric acid and decreased urinary phosphate and pH; factors which strongly favor ammonium urate calculi [168, 171]. It has been shown that an increase in urinary ammonia occurs in babies whose feeds consisted predominantly of rice [168]. Furthermore, urinary bladder stones have been reported to be common in Australian aboriginal children in which breast feeding is supplemented with white flour and little else [172]. Bladder stone disease in children was endemic in 19th-century England, and it has been suggested that the exclusive substitution of breast milk with porridge and bread was a significant factor in the pathogenesis of this disease [173]. Endemic childhood bladder disease clearly occurs in countries and populations in which cereal grains comprise most of the caloric

intake, and cereal grains have been implicated in the etiology of the disease [168, 172]. However, it is likely that other factors, including calorie and protein malnutrition, infection and starvation operate synergistically with high intake of cereal grains to elicit the disease [174] (fig. 3).

Antinutrients in Cereal Grains

In the evolution of plant life history strategies, plant species encounter a basic dilemma in the amount of adaptational energy they must allocate to growth versus that which they must allocate to defenses necessary for survival in the presence of pathogens and herbivores [175]. Therefore, plants face an evolutionary tradeo ; they must grow fast enough to compete, yet they must also divert enough energy for the synthesis of secondary metabolites required to ward o pathogens and herbivores. Defense is not the only role of secondary metabolites, and other functions include attraction of pollinators, protection from ultraviolet light, structural support, temporary nutrient storage, phytohormone regulation, facilitation of nutrient uptake and protection of roots from acidic and reducing environments [175]. Quite frequently, plants provision seeds with high concentrations of secondary metabolites to ensure the survival of the seed and the rapidly growing seedling before it can synthesize its own secondary compounds.

Cereal grains which are the seeds of grasses (gramineae) contain a variety of secondary metabolites which can be either toxic, antinutritional, benign or somewhere in between, dependent upon the physiology of the consumer animal. The presence of secondary metabolites in plants do not guarantee freedom from predation by herbivores, and many herbivores have evolved a number of strategies for circumventing the resistance mechanisms of their hosts [175]. Many birds, rodents, insects and ruminants can clearly consume cereal grains in high quantities with minimal undue e ects. Because primates evolved in the tropical forest, all of their potential plant food was derived from dicotyledonous species; therefore, the primate gut was initially adapted to both the nutritive and defensive components of dicotyledons rather than the nutritive and defense components of monocotyledonous cereal grains [176]. Under certain conditions a few species of primates (*Papio* species, *Theropithecus gelada*) have been observed to consume grass and grass seeds; however, by and large, consumption of monocotyledonous plant foods, particularly cereal grains, is a notable departure from the traditional plant foods consumed by the majority of primates [176]. Consequently, humans, like all other primates have had little evolutionary experience in developing resistance to secondary and antinutritional compounds which normally occur in cereal grains.

Alkylresorcinols

Alkylresorcinols are phenolic compounds which are found in the highest amounts in rye (97 mg/100 g), in high amounts in wheat (67 mg/100 g) and in lower amounts in other cereals such as oats, barley, millet and corn [177]. These compounds are concentrated in the outer bran layers of cereal grains and are thought to provide resistance from pathogenic organisms during dormancy and germination [178]. Alkylresorcinols previously were associated only with rye and were thought to be a problem only in animal nutrition. Feeding of rye in large amounts to cattle, sheep, horses, pigs and poultry has been shown to cause slower growth than feeding of other cereal grains [177]. Subsequent studies indicated the growth depressive e ects of alkylresorcinols could be attributed to both an appetite depressive e ect (70%) and a direct toxic e ect (30%) [179].

Although there is scant information upon the e ects of alkylresorcinols in human nutrition, in animal models they have been shown to cause red-cell blood hemolysis, permeability changes of erythrocytes and liposomes, DNA strand scission, and have been shown to be involved in many pathological conditions including hepatocyte and renal degeneration [177]. An in vitro experiment in humans has shown that alkylresorcinols were able to stimulate platelet thromboxane (TXA_2) production by 30–65% using 0.02–2.0 mmol/l concentrations. To date no human experiments have been conducted to determine if these proinflammatory e ects can occur in vivo from alkylresorcinols ingested from whole grain wheat products. It should be pointed out that cereal grain alkylresorcinols may have antimutagenic activity [181], and in lower concentrations may have antioxidant properties [182].

Alpha-Amylase Inhibitors

The aqueous/saline protein extract of wheat seed is called the albumin fraction. Within the albumin fraction are a very large number of protein components capable of inhibiting alpha-amylases from insect, mammalian, avian and marine species. Alpha-amylase inhibitors make up as much as 80% of the total albumin fraction and may represent 1% of wheat flour [183]. Because of their thermostability, alpha-amylase inhibitors persist through bread baking and are found in large amounts in bread, breakfast cereals, pasta and other wheat products [183]. Alpha-amylase inhibitors are ubiquitous in the cereal family (gramineae) and in addition to their presence in wheat, they have been found in rye, barley, oats, rice and sorghum. As with alkylresorcinols, alpha-amylase inhibitors are thought to have evolved in cereal grains as a defense mechanism against herbivore predation, primarily against insects [184].

The multiple alpha-amylase inhibitors found in cereal grains have distinctive structural properties and show considerable variability in their inhibitory

e ect upon human salivary and pancreatic alpha-amylase [185, 186]. Because salivary and pancreatic amylases catalyze the hydrolysis of glycosidic linkages in starch and other related polysaccharides, their inhibition by cereal grain alpha-amylase inhibitors have been theorized to have beneficial therapeutic e ects by reducing carbohydrate-induced hyperglycemia and hyperinsulinemia [187]. Early studies of commercially available alpha-amylase inhibitor preparations failed to decrease starch digestion in humans [188, 189] perhaps because of insu cient antiamylase activity [190]. More recent research utilizing purified amylase inhibitors have demonstrated that these antinutrients can rapidly inactivate amylase in human intestinal lumen [186, 190] in a dose-dependent manner [186] and reduce postprandial rises in glucose and insulin [191].

Although the acute e ects of alpha-amylase inhibitors may appear to have therapeutic benefit in patients su ering from diabetes mellitus, obesity and other diseases of insulin resistance, chronic administration in animal models has been shown to induce adverse e ects including deleterious histological changes to the pancreas and pancreatic hypertrophy [192]. Because it is unclear if these dietary antinutrients can elicit similar deleterious changes in the pancreatic structure and function of humans [193], the presence of alpha-amylase inhibitors in human foodstu s is generally considered to be undesirable [183].

In addition to their influence upon starch digestion, alpha-amylase inhibitors are known to be prominent allergens. The inhalation of cereal flours is the cause of baker's asthma, an occupational allergy with a high prevalence in the baking industry [194]. Baker's asthma is mediated by IgE antibodies, and until recently the identification of the IgE binding proteins (allergens) in the putative cereal flours was unknown. Over the past decade, it has been conclusively demonstrated that a variety of alpha-amylase inhibitor proteins are responsible for bakers' allergenic reaction to cereal flours [194, 195]. Further, alpha-amylase inhibitors recently have been demonstrated to be a relevant allergen in children experiencing hypersensitivity reactions following wheat ingestion [196].

Protease Inhibitors

Protease inhibitors are proteins which have the ability to inhibit the proteolytic activity of certain enzymes and are common throughout the plant kingdom, particularly among the legumes. As with alpha-amylase inhibitors, there are a muiltiplicity of plant proteins which have protease inhibitor activity. The two best-studied protease inhibitors, derived from plants, are the Kunitz inhibitor, which has a specificity directed mainly towards trypsin in human gastric juice, and the Bowman-Birk inhibitor which is capable of inhibiting chymotrypsin as well as trypsin. The Bowman-Birk inhibitor is relatively stable

to both heat and digestion and can therefore survive intact through cooking and transit through the stomach [197].

Normally, there is a negative feedback loop whereby the secretory activity of the pancreas is controlled by the level of trypsin in the intestinal tract. Intraluminal trypsin inhibits pancreatic secretion by inhibiting the release of the hormone cholecystokinin from the intestinal mucosa; however when dietary protease inhibitors bind trypsin, there is an uncontrolled release of cholecystokinin. This continuous and excessive release of cholecystokinin has been shown in animal models to result in pancreatic hypertrophy and hyperplasia [198] and may eventually lead to cancer [199]. The deleterious influence of the Bowman-Birk inhibitor upon this negative feedback loop has been demonstrated in humans [200].

As with other secondary metabolites, the primary function of protease inhibitors in plants is thought to prevent predation from invading insects and microbes [201]. Protease inhibitors have been found in virtually all of the cereal grains [201]; however, they apparently have low trypsin inhibitory activity. Wheat has been shown to have only 1.5% the trypsin inhibitory activity of soy beans [202]. Nonetheless, feedings of raw rice bran [201] and raw rye and barley [203] have resulted in pancreatic hypertrophy in broiler chicks which was attributable to protease inhibitors. In humans, the dietary e ects of chronic low level exposure to plant protease inhibitors are unknown, and there is some evidence that they may have beneficial, antineoplastic e ects [204].

Lectins

Lectins are proteins that are widespread in the plant kingdom with the unique property of binding to carbohydrate-containing molecules, particularly toward the sugar component. They were originally identified by their ability to agglutinate (clump) erythrocytes which occurs because of the interaction of multiple binding sites on the lectin molecule with specific glycoconjugate receptors on the surface of the erythrocyte cell membranes. Because of this binding property, lectins can interact with a variety of other cells in the body and are recognized as the major antinutrient of food [205].

Of the eight commonly consumed cereal grains, lectin activity has been demonstrated in wheat, rye, barley, oats, corn [206], and rice [207] but not in sorghum or millet [208]. The biological activity of lectins found in cereal grains are similar because they are closely related to one another both structurally and immunologically [209]. The best studied of the cereal grain lectins is wheat germ agglutinin (WGA), and the in vitro biological e ects of WGA upon tissues and organs are astonishingly widespread. Virtually every cell in the body, and every extracellular substance can be bound by WGA because of

the ubiquity of secreted glycoconjugates [210]. In his comprehensive review, Freed [210] has shown that WGA can bind (in vitro) the following tissues and organs: alimentary tract (mouth, stomach, intestines), pancreas, musculoskeletal system, kidney, skin, nervous and myelin tissues, reproductive organs, and platelets and plasma proteins.

WGA is heat stable and resistant to digestive proteolytic breakdown in both rats [211] and humans [212] and has been recovered intact and biologically active in human feces [212]. WGA and lectins in general bind surface glycans on gut brush border epithelial cells, and the damage they cause to these cells interferes with digestive/absorptive activities, stimulates shifts in bacterial flora and modulates the immune state of the gut [213]. In rats, WGA has been shown to cause hyperplastic and hypertrophic growth of the small intestine and interfere with normal gut metabolism and function, while simultaneously inducing pancreatic enlargement and thymic atrophy [211]. The dietary levels of WGA (7 g/kg body weight) necessary to induce these untoward e ects in rats is significantly higher than dietary levels of WGA which would be normally encountered in foods derived from wheat, since the concentration of WGA is about 2 g/kg in unprocessed wheat germ [212]. No long-term studies of low level WGA ingestion upon gut structure and function have been conducted in humans; however there is suggestive evidence that high wheat gluten diets induce jejunal mucosal architectural changes in normal subjects without celiac disease [214].

Most food proteins entering the small intestine are fully degraded into their amino acid components and therefore do not pass intact into systemic circulation. However, it is increasingly being recognized that small quantities of dietary protein which escape digestive proteolytic breakdown can be systemically absorbed and presented by macrophages to competent lymphocytes of the immune system [215, 216]. Under normal circumstances, when the luminal concentrations of intact dietary proteins is low, absorbed proteins generally elicit a minimal allergic response because of the limiting influence of T-suppressor cells. Because of their resistance to digestive, proteolytic breakdown, the luminal concentrations of lectins can be quite high, consequently their transport through the gut wall can exceed that of other dietary antigens by several orders of magnitude [216]. Additionally, WGA and other lectins, may facilitate the passage of undegraded dietary antigens into the systemic circulation by their ability to increase the permeability of the intestine [217]. Consequently, dietary lectins represent powerful oral immunogens capable of eliciting specific and high antibody responses [213]. In rats, dietary WGA is rapidly transported across the intestinal wall into systemic circulation where it is deposited in blood and lymphatic vessel walls [211]. Although no direct human experiments have been conducted evaluating dietary WGA passage

into systemic circulation, there is substantial evidence to indicate that this event occurs since serum antibodies to WGA are routinely found in normals [218, 219] and in celiac patients [219].

Once WGA crosses into systemic circulation, it has the potential to interfere with the body's normal hormonal balance, metabolism and health [210, 213]. Numerous in vitro studies have shown WGA to have insulomimetic e ects [220, 221]. Although few animal and no human studies have been designed to evaluate the in vivo influence of dietary WGA upon insulin metabolism, experiments utilizing dietary kidney bean lectin (PHA) in rats have demonstrated a depression in circulating insulin levels which modulates complex change in the body's hormonal balance [213]. Numerous in vitro studies suggest that WGA may have the potential to subtly impact health via its ability to inhibit the mitogenic actions of multiple peptide growth factors including insulin-like growth factor (IGF) [222], platelet-derived growth factor [222], epidermal growth factor [222, 223] and nerve growth factor [224]. Children with celiac disease exhibit short stature and stunted growth patterns [225], depressed levels of IGF-I [226–228], depressed levels of IGF-binding protein 3 (IGFBP-3) [226, 227] and lower levels of growth hormone binding protein II (GH-BP II) [226]. Administration of wheat (gluten)-free diets in celiac children increases circulating levels of IGF-I [226, 227], IGFBP-3 [226, 228] and GH-BP II [226] while simultaneously improving height and weight [226]. Presently, there is insu cient data in humans to determine the health ramifications of chronic low level consumption of WGA, but because detectable amounts of functionally and immunochemically intact WGA are transported across the intestinal wall [211], the potential for this lectin to disrupt human health is high.

Autoimmune Diseases and Cereal Grain Consumption

Autoimmune diseases occur when the body loses the ability to discriminate self proteins from nonself proteins. This loss of tolerance ultimately results in destruction of self tissues by the immune system. Autoimmune diseases occur in a variety of tissues and include such well-known maladies as rheumatoid arthritis, multiple sclerosis, and insulin-dependent diabetes mellitus (IDDM). Typically, autoimmune diseases are characterized by the presence of autoantibodies against specific self proteins [229]. Most autoimmune diseases are thought to develop via an interaction of an environmental factor or factors in conjunction with a specific hereditary component.

Dietary cereal grains are the known environmental causative agent for at least two autoimmune diseases: celiac disease [230] and dermatitis herpeti-

formis [231]. Withdrawal of gluten-containing cereals from the diet ameliorates all symptoms of both diseases. Further, evidence from clinical, epidemiological and animal studies implicate cereal grains in the etiology of other autoimmune diseases. The mechanism or mechanisms by which cereal grains may induce autoimmunity in genetically susceptible individuals is not clearly defined; however it is increasingly being recognized that the process of molecular mimicry, by which a specific foreign antigen may cross react with self antigens, may be involved in a variety of autoimmune diseases [232, 233]. Additionally, cereal grain lectins and proteins may also have involvement in the development of autoimmunity via their modulation of immune system components [234, 235].

Autoimmunity

The development of autoimmunity is a poorly understood process; however it is generally agreed that it occurs as a result of an interaction between environmental and genetic components [229]. The genetic component most closely associated with the expression of autoimmune diseases are those genes which code for the human leukocyte antigens (HLA). The HLA is subdivided into class I (HLA-A, HLA-B, HLA-C), class II (HLA-DR, HLA-DQ and HLA-DP) and class III categories. Both class I and class II proteins are transmembrane cell surface glycoproteins which are required for the recognition of both self and foreign antigens by T lymphocytes. Class I proteins are found on all nucleated cells and platelets, whereas class II HLAs are found on macrophages, monocytes, epithelial dendritic cells, B lymphocytes and activated T lymphocytes. Class I HLA proteins present peptide fragments from degraded intracellular viruses to circulating CD8+ cytotoxic lymphocytes which recognize and attack virus-infected cells. Class II HLA proteins present foreign antigens to CD4+ T lymphocytes which results in the induction of T-cell proliferation, lymphokine production, and subsequent synthesis of immunoglobulin by B lymphocytes. Except for human spondyloarthropathies, the preponderance of known or suspected autoimmune diseases are associated with class II haplotypes [229].

Many tissues (thyroid, adrenal, pancreatic islet beta cells, bile ducts, kidney, etc.) that are typically attacked by autoimmune diseases do not normally express class II HLA antigens, consequently, it is paradoxical that autoimmunity should develop in these tissues. The induction of inappropriate class II antigens in nucleated cells may be an important preliminary event in the etiology of autoimmune disease [236] and can occur from the stimulatory e ect of interferon-γ (IFN-γ) wrought by viral infections [210]. Additionally, lectins are potent inducers of HLA class II molecules [237], probably via their ability to stimulate release of IFN-γ [238, 239]. Further, the gliadin fraction of wheat, which exhibits lectin

activity [240], has been shown to amplify HLA class II expression in intestinal epithelial cell lines [235]. Ingested WGA from dietary wheat products, crossing the intestinal barrier would also influence the development of autoimmunity by its ability to stimulate T-lymphocyte proliferation [234, 241].

Molecular Mimicry

In autoimmune disease, the inability of the immune system to distinguish self antigens from foreign antigens ultimately results in the destruction of self tissues. There is now a substantial body of evidence indicating that the breaking of tolerance to self antigens can occur when invading foreign proteins contain amino acid homologies similar to a protein in the host [233, 242]. This similarity in structure shared by products of dissimilar genes (dubbed molecular mimicry) causes cross-reactive immune responses which are directed not only at the invading foreign protein but also at any cells displaying amino acid sequences similar to those of the foreign protein. The main body of evidence implicates viral and bacterial pathogens as initiators of cross reactivity and autoimmunity [233, 242]; however there is an emerging body of literature supporting the view that dietary antigens [243, 244], including cereal grains [245, 246], may also induce cross-reactivity and hence autoimmunity by virtue of peptide structures homologous to those in the host.

Genetic and Anthropological Factors

Virtually all autoimmune diseases have a strong genetic component categorized by a variety of HLA haplotypes [229]. For instance, there is a 73% greater risk of developing celiac disease in people displaying the HLA-DQ2 antigen relative to those who do not [229]. It is not entirely clear why HLA genes alter the relative risk for autoimmune disease; however it is likely that they influence the binding a nity of the HLA peptide complex with circulating T lymphocytes. Because the protein subunits comprising the HLA antigen binding groove are coded by highly polymorphic HLA genes [229], various HLA alleles can subtly alter the structure of the HLA antigenic binding groove [247] and therefore influence whether a mimicking epitope has a proliferative or anergizing response upon engagement of the HLA peptide complex with the T-cell receptor. From an evolutionary perspective, the inheritance of specific HLA haplotypes appears to be primarily related to infectious disease susceptibility, and inheritance of certain HLA haplotypes may have conferred relative protection from invading pathogens [248, 249].

In celiac disease, there is a general geographical northwest (NW) to southeast (SE) disease incidence gradient from the Near East to Northern Europe [249]. Associated with this gradient is a concurrent NW/SE gradient for the HLA-B8 antigen which parallels the spread of agriculture and hence cereal

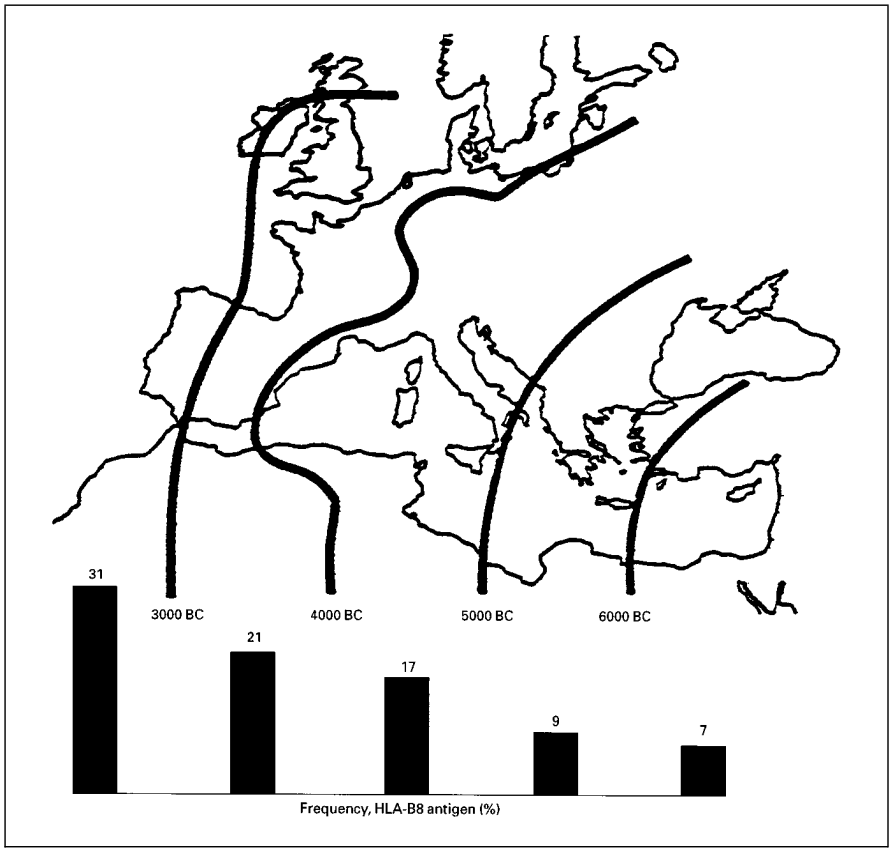

Fig. 4. HLA-B8 frequencies and the spread of agriculture in Europe. Adapted from Simoons [249].

grain consumption (wheat and barley) from the Near East 10,000 years ago (fig. 4). HLA-B8 is not a direct marker for celiac disease, but because it is in linkage disequilibrium with HLA-DQ2, it is directly implicated with the disease. Consequently, high frequencies of HLA-B8 (which are positively associated with celiac disease via their close linkage with HLA-DQ2) occur in European populations with the least evolutionary exposure to cereal grains, and conversely, those populations with the most evolutionary exposure to cereal grains maintain lower frequencies of HLA-B8 [249, 250]. It has been suggested that this gradient occurs because high frequencies of HLA-B8 and hence HLA-DQ2 were once typical of Near Eastern peoples; however these antigens became a liability with the advent of regular cereal grain consumption

ushered in by the agricultural revolution [249, 250]. Because cereal grain consumption presumably would have increased mortality (via increased susceptibility to celiac disease) in populations with HLA-DQ2, natural selection would have reduced the frequency of this antigen in populations with the most evolutionary exposure to wheat and barley [249, 250].

Because of the strong linkage disequilibrium for the genes which code for the (B8, DR3, DQ2) haplotype, autoimmune disorders linked with DR3, including IDDM, have been found more often in celiac disease patients [251]. The incidence of IDDM is approximately 7–10 times higher in celiacs than in the normal population [252, 253], and the incidence of IDDM, like celiac disease, is found in Europe in a general NW/SE gradient [254]. Both milk [243, 255] and wheat [255], contain dietary components which would have increased in European populations adopting agriculture, and have been suspected elements in the pathogenesis of IDDM.

Autoimmune Diseases Associated with Cereal Grain Consumption

There are a number of autoimmune diseases in which cereal grains have been implicated. In a few of these diseases (celiac disease and dermatitis herpetiformis), there is a 100% certainty that cereal grains are the causative agent, whereas in others the link is not so strong. Because of the increased incidence [251] of other, simultaneously occurring autoimmune diseases in celiac patients (table 9), many of these maladies have been examined to determine, what role, if any, cereal grains may play in their etiology.

Celiac Disease. Marsh [256] stated: 'Despite the central importance of wheat as a dietary staple throughout the world, it is astounding that its presumptive role in precipitating celiac sprue disease was discovered only 40 years ago by the Dutch pediatrician W.K. Dicke.' Indeed, it is 'astounding' that humanity was unaware, until only relatively recently, that an ordinary and commonplace food such as cereal grains could be responsible for a disease which a icts between 1 and 3.5 people per 1,000 in Europe [257]. The precise mechanism by which certain peptide sequences in the alcohol-soluble fraction (gliadin) of wheat, rye and barley elicit celiac disease is still poorly understood [258]. However, there is an increasing consensus that celiac disease is an autoimmune disease [230, 259], mediated by T lymphocytes within the lamina propria which damage intestinal villi.

It is probable that the process of molecular mimicry is involved in the development of celiac disease [232]. Kagno et al. [260] have shown that wheat alpha-gliadin shares an amino acid sequence homology with the E1B protein of human adenovirus 12 (Ad-12) and that antibodies directed against E1B cross-react with alpha-gliadin. Since 89% of patients with celiac disease, versus 17% of controls, showed evidence of Ad-12 infection [260], it is possible that

Ad-12 infection in individuals genetically predisposed to celiac disease (HLA-DQ2) may facilitate development of the disease by virtue of cross-reactivity, perhaps by three-way mimicry among the two foreign antigens (Ad-12, gliadin), the target tissue and even HLA proteins, themselves [261].

Celiac disease is typically screened by detection of circulating IgG antibodies to reticulin (ARA), endomysium (AMA) or gliadin (AGA). Endomysium is the connective tissue surrounding smooth muscle fibers of the gut, whereas reticulin are fibrils connecting smooth muscle cells and elastic tissue within endomysium. The specific protein or proteins (autoantigen) within reticulin and endomysium to which ARA and AMA are directed is unclear; however recent studies have indicated both transglutaminase [262] and calreticulin [245] are likely candidates. It has been shown that gliadin and calreticulin share homologous amino acid sequences with one another, and anticalreticulin antibodies cross react with gliadin [245], thereby supporting the concept that celiac disease involves molecular mimicry [263]. Because gliadins are a complex mixture of proteins that contain at least 40 di erent components in a single variety of wheat [264], it is unlikely that a single gliadin protein causes celiac disease, but rather several prolamines that express similar or identical epitopic domains [265]. Thus, it is likely that multiple gliadin proteins can cross react with at least one and probably more autoantigens in celiac disease, similar to that observed in other autoimmune diseases [246]. The self antigen with the closest molecular structure (following HLA presentation) to the mimicking foreign peptide will likely be primarily responsible for the destructive autoimmune response wrought by T lymphocytes.

A general overview of celiac disease would then suggest that dietary WGA bound to enterocytes increases the permeability of the gut [217], thereby allowing entry of both WGA [211] and other gliadin proteins into systemic circulation. WGA or perhaps gliadin, by virtue of their lectin properties, induce the inappropriate expression of HLA class II molecules, which may present a variety of internally processed proteins (including calreticulin), on the surface of intestinal epithelial cells [235]. In genetically susceptible individuals (HLA-DQ2), the molecular conformation of the HLA antigenic binding groove is subtly altered [247] so that the presentation of the internally processed, mimicking protein (calreticulin) causes a proliferative rather than anergizing response upon engagement with the T-cell receptor. Circulating gliadin proteins are engulfed by macrophages which then present the processed gliadin peptide fragments, via HLA molecules, to CD4+ T lymphocytes. Because these gliadin peptide fragments presented by the macrophage have amino acid sequences homologous to those of the endogenous protein (calreticulin), which is artificially expressed upon the surface of intestinal epithelial cells by cereal grain lectin stimulation, cytotoxic CD4+ T lymphocytes initiate an immune re-

sponse both upon the macrophage expressing fragments of the foreign peptide (gliadin) as well as upon the intestinal epithelial cell expressing the homologous, endogenous protein (calreticulin). Viruses suspected of causing autoimmune disease operate in a likewise manner to induce the inappropriate expression of autoantigens, including calreticulin [266] on the cell surface, as well as maintaining structural homology to a self antigen [233, 242]. Once the mimicry process begins, the destructive autoimmune response may be further enhanced by the ability of WGA [234, 241] or viruses [210] to induce T-cell proliferation, mediated by either lectin [238, 239] or viral [210] IFN-γ stimulation.

Dermatitis Herpetiformis. Dermatitis herpetiformis (DH) is characterized as an intensely itching papulovesicular skin disease diagnosed by IgA deposits in the basement membrane [267]. DH can be successfully treated by a gluten-free diet, although it may take years before the dermatitis is fully controlled by diet only [231]. DH and celiac disease share a common genetic basis (HLA-DQ2), and approximately 60% of DH patients have moderate to severe small-bowel villous atrophy [251]. As with celiac disease, the precise tissue autoantigen in DH is unclear. However, there are similar structural homologies between human elastin and high-molecular weight glutenin (a wheat gluten protein) which have been shown to cause IgA cross-reactivity of the two proteins in human serum [268]. Bodvarsson et al. [268] have suggested that DH may be due in part to this cross-reactivity (mimicry) between dietary glutenin and dermal elastin.

Insulin-Dependent Diabetes mellitus. IDDM is a complex disease involving numerous putative environmental factors; however it has been suggested that shared amino acid sequences (i.e. molecular mimicry) between viral proteins and pancreatic beta-cell proteins (e.g. coxsackie virus protein and glutamate decarboxylase) represent a likely mechanism causing the disease [269]. In addition to viral proteins, dietary proteins in cow's milk cross react with a beta-cell antigen and are therefore suspected environmental etiologic agents [243]. However, as pointed out by Schatz and Maclaren [270], the feeding of wheat in animal models of IDDM elicits a greater incidence of the disease than does milk. Numerous studies have demonstrated that feeding of wheat gluten to rats or mice, which are genetically predisposed to IDDM, increases the expression of the disease [255, 271, 272]. It remains elusive how wheat proteins increase the expression of IDDM in genetically predisposed animals. Because Ro/SS-A autoantibodies are found in nonobese (NOD) diabetic mice [273] and in humans with IDDM [274] and in humans with both IDDM and Sjogren's syndrome [275], the molecular mimicry which occurs between calreticulin and wheat gliadin peptides [245] may be involved in the autoimmune response. Although there is conflicting data regarding calreticulin's role in the Ro/SS-A complex [276], recent evidence unequivocally shows that

calreticulin exists in a form directly associated with all four varieties of human Ro/SS-A RNA molecules [276].

Sjögren's Syndrome. Sjögren's syndrome is an autoimmune disease characterized by lymphocytic infiltration of CD4+ T cells into salivary and lachrymal glands leading to symptomatic dry eyes and mouth [278]. Circulating antibody levels of gliadin and a reticulin glycoprotein have been found to be higher in patients with Sjögren's syndrome than in controls [279]. Furthermore, Sjögren's syndrome occurs at a level approximately 10 times higher in celiac subjects than in normals [280]. Ro/SS-A autoantibodies are typically elevated in Sjögren's syndrome [275, 278], and because the four cytoplasmic RNA components of Ro/SS-A (hY RNA 1,3,4,5) exist together with a form of calreticulin [277], the molecular mimicry between alpha-gliadin and calreticulin [245] may in part be responsible for the autoimmune response. Calreticulin is normally a cytolsolic protein, however viral infection has been shown to increase its cell-surface expression [266]. In a similar manner, lectins (including gliadin) are known to induce inappropriate expression of HLA class II molecules at nucleated cell surfaces [235, 237].

In Sjögren's syndrome an additional suspected autoantigen, termed BM180, has been isolated from basement membrane in the lacrimal and parotid exocrine secretory glands, and which cross-reacts with alpha-gliadin proteins [246]. Astonishingly, BM 180 contains an N-terminal amino acid sequence (VRVPVPQLQPQNP) identical to that found in alpha-gliadin, and mono- and polyclonal antibody data therefore suggest that BM 180 is a mammalian form of gliadin [246]. Because BM 180 may be required for stimulus secreting coupling by lacrimal acinar cells [246], autoimmune attacks by CD4+ T cells, primed by previous interaction with macrophages presenting alpha-gliadin, would be directed, via molecular mimicry, at lacrimal and parotid cells inappropriately presenting BM 180. Despite the suggestive link between celiac disease and Sjögren's syndrome, as well as the molecular mimicry evidence, there are scant clinical trials evaluating the e ectiveness of gluten-free diets in Sjögren's syndrome.

Rheumatoid Arthritis. Rheumatoid arthritis is a complex autoimmune disease involving numerous environmental and genetic components, and similar to a number of other autoimmune diseases is found more often in celiac patients [251, 281]. Multiple studies of arthritic patients have demonstrated elevated antibody levels for gliadin [282, 283], and gluten-freee diets have been shown to be e ective in reducing arthritic symptoms in celiac patients [283–285]. No large clinical trials have been undertaken to specifically examine the e ectiveness of gluten-free diets in the treatment of arthritis; however there are numerous case studies reporting alleviation of arthritis symptoms with grain-free diets [286–289]. Additionally, complete withdrawal of food during fasting reduces objective and subjective indices of the disease [290].

Because serum antibodies in arthritic patients recognize the antigen, bovine serum albumin (BSA) from cow's milk, and since BSA contains homologous amino acid sequences with human collagen type I, Clq, it has been suggested that molecular mimicry represents a potential mechanism by which milk consumption may trigger arthritis [291]. In addition to milk, glycine-rich cell wall protein (GRP 1.8), which is ubiquitous in cereal grains and legumes, shares significant amino acid homology with fibrillar collagen and procollagen and has been shown to stimulate T cells from the synovial fluid of juvenile and adult rheumatoid arthritis patients [292]. A third dietary antigen which may also induce rheumatoid arthritis via molecular mimicry is the alpha-gliadin component of wheat which shares significant amino acid sequences with calreticulin [245]. Anticalreticulin antibodies have been found in rheumatoid arthritis patients [293], and HLA-DR4 molecules from arthritic patients are known to present a peptide fragment derived from calreticulin [294]. Dietary antigens from three food sources (milk, grains and legumes) contain multiple peptides which mimic those found in joint tissue from arthritis patients, whereas grains and legumes additionally contain lectins which can induce inappropriate presentation of HLA class II molecules [235, 237], consequently, future dietary interventions aimed at reducing arthritis symptoms would need to consider these potential confounding e ects.

Other Autoimmune Diseases. IgA nephropathy is the most common form of primary glomerulonephritis worldwide, and about one quarter of these patients progress to terminal renal failure 10 years after the apparent clinical onset [295]. IgA nephropathy is characterized by deposition of circulating IgA-containing immune complexes (IgAIC) in the mesangium. IgA nephropathy patients maintain increased intestinal permeability [296], elevated circulating antibodies to gliadin [296, 297], and have serum that contains exogenous lectins which induce interleukin-6 (IL-6), a nephritogenic cytokine [298]. In rodent models, IgA nephropathy can be induced by gliadin-containing diets and have been shown to significantly increase both gliadin antibodies and IgA mesangial deposits compared to gliadin-free controls [299]. Humans following gluten-free diets have shown reduced IgA antigens and reduced levels of IgAIC, however these diets do not appear to alter the progression towards renal failure [300]. Amore et al. [240] have suggested that gliadin, because of its lectin activity may favor the binding of IgA and IgAIC to mesangial cells, thereby enhancing both IgA mesangial trapping and in situ IgA deposit formation.

The cause of recurrent aphthous stomatitis (canker sores) is unknown; however it is suspected to be mediated by immunological mechanisms interacting with an undefined target tissue [301]. O'Farrelly et al. [302] have shown that 4 of 11 aphthous stomatitis patients had raised levels of antibodies to

alpha-gliadin, and in 3 of these 4 subjects, the ulceration remitted on a gluten-free diet and relapsed upon gluten challenge. Other studies of aphthous stomatitis patients have shown favorable responses to gluten-free diets in some, but not all aphthous stomatitis patients [303, 304]. The mechanism by which wheat gluten is associated with the development of aphthous ulcerations is unclear.

There is increasing recognition that molecular mimicry is a highly likely mechanism underlying the development of multiple sclerosis [305, 306]. A number of viral and bacterial proteins have been shown to cross react with myelin basic protein (MBP) [305], one of the suspected target antigens in multiple sclerosis (MS). Because the blood-brain barrier limits access to the CNS to activated T cells, invasion of the CNS requires autoreactive T cells to be stimulated in the peripheral immune system. Therefore, it is possible that dietary antigens causing persistent T-cell stimulation, and bearing similar amino acid homologies to the various myelin and nonmyelin target antigens, could cause polyclonal expansion of autoreactive T cells in the periphery, in a manner similar to that observed for bacterial and viral antigens. Although no homologous amino acid sequences have yet been identified between dietary antigens and suspected autoantigens in MS patients, there are epidemiological reports which link both wheat [307] and milk [308] consumption to the incidence of multiple sclerosis, consistent with the observations that MS is positively correlated to latitude [309]. There are a number of case reports showing remission of MS on gluten-free diets [310–312]. Furthermore, some MS patients have altered intestinal mucosa [313, 314], suggestive of increased intestinal permeability to dietary antigens. However, MS patients generally do not show increased antibodies to gliadin [315], and a number of case studies have not shown beneficial e ects of gluten-free diets [316, 317]. If dietary antigens containing amino acid sequences similar to putative self antigens, indeed, do stimulate peripheral T cells, then interventions evaluating the influence of diet upon MS would need to consider the potential confounding influence of multiple dietary antigens (dairy products, grains, legumes, and yeast) capable of either molecular mimicry and/or T-cell stimulation.

Psychological and Neurological Illnesses Associated with Cereal Grain Consumption

Neurological complications have long been recognized in celiac patients and can include epilepsy, cerebellar ataxias, dementia, degenerative central nervous system disease, peripheral neuropathies (of axonal or demyelinating type), and myopathies [318]. A recent study showed that 57% of patients

with neuropathies of unknown cause (25 ataxia, 20 peripheral neuropathy, 5 mononeuritis multiplex, 4 myopathy, 3 motor myopathy, 2 myelopathy) demonstrated positive titres for antigliadin antibodies, and 16% (40 times higher than the general population) of this group also had celiac disease [315]. The cause of neurological dysfunction associated with celiac disease and antigliadin antibodies is unknown; however it has been suspected that an immunological mechanism may be involved [315, 318]. Although no clinical trials have yet been conducted of strict adherence to a gluten-free diet, it has been suggested that such a diet may result in stabilization or even improvement of neurological dysfunction [315].

Epilepsy is observed in 5.5 of 100 cases of celiac disease, and in about half of these patients bilateral parietooccipital calcifications are found in the cortical or subcortical areas [319]. This triple association has a common HLA haplotype and is thought to occur via an underlying immunological disorder [320]. If gluten-free diets are adopted soon after the onset of epilepsy, seizures can be severely reduced or eliminated [321, 322].

The behavioral syndrome of autism in children is characterized by few or no language and imaginative skills, repetitive and self-injurious behavior and abnormal responses to human and environmental stimuli. The cause of the syndrome is poorly understood, however it is thought that both genetic [323] and immunological factors [324] may be involved. Autistic children maintain HLA haplotypes [323] that frequently occur in other autoimmune diseases including rheumatoid arthritis, and they display autoantibodies to myelin basic protein [324]. Some autistic patients have been shown to have increased antibodies to gluten and casein [325]; however, the amelioration of symptoms in response to gluten-free diets has been equivocal [325, 326].

It has been more than 30 years since Dohan first formulated the hypothesis that opioid peptides found in the enzymatic digests of cereal grain gluten are a potentiating factor evoking schizophrenia in susceptible genotypes [327, 328]. In a meta-analysis of the more than 50 articles regarding the role of cereal grains in the etiology of schizophrenia published between 1966 and 1990, Lorenz [329] concluded: 'In populations eating little or no wheat, rye and barley, the prevalence of schizophrenia is quite low and about the same regardless of type of acculturating influence.' In support of this conclusion are multiple clinical studies [330–332] which have shown that schizophrenic symptoms improved on gluten-free diets and worsened upon reintroduction. Furthermore, the incidence of schizophrenia is about 30 times higher in celiac patients than in the general population [329], and schizophrenics have elevated circulating IgA antibodies to gliadin [333].

There is increasing recognition that in a subset of schizophrenic patients, autoimmune mechanisms are involved in the etiology of the disease [334,

335]. Schizophrenics maintain several immunological abnormalities including increased prevalence of autoimmune disease and antinuclear and other autoantibodies, decreased lymphocyte interleukin-2 (IL-2) production, increased serum IL-2 receptor concentration, increased serum IL-6 concentrations and an association with HLA antigens [334, 335]. Similar to other autoimmune diseases, cereal grains may potentiate their putative autoimmune e ects in schizophrenia via molecular mimicry in which self antigens in brain tissue are recognized and destroyed by autoaggressive T lymphocytes because of the structural similarity between brain antigens and foreign dietary antigens. Although this hypothesis may be operative in some schizophrenics, the rapid remission of symptoms by gluten-free diets, observed in clinical trials [330–332], is suggestive that an acute mechanism may be additionally responsible, since it is unlikely that damaged neuronal cells could regenerate in such a short time frame. In this regard, it has been long recognized that certain gluten peptides derived from wheat have high opioid-like activity that is naloxone reversible [336, 337]. The structural identity of these opioid peptides derived from the enzymatic digest of wheat gluten have recently been characterized and sequenced [338–340], and there is significant evidence utilizing radiolabelled gliadin isotopes to show that these peptides reach opioid receptors in the brain and peripheral organs [329]. Thus, it is possible that cereal grains may elicit behavioral changes via direct interaction with central nervous system opioid receptors or perhaps via simultaneous immune-mediated reactions against central nervous system antigens.

Conclusions

From an evolutionary perspective, humanity's adoption of agriculture, and hence cereal grain consumption, is a relatively recent phenomenon. Table 3 shows that this event occurred in most parts of the world between 5,500 and 10,000 years ago. Cereal grains represent a biologically novel food for mankind [341, 342], consequently there is considerable genetic discordance between this staple food, and the foods to which our species is genetically adapted.

Cereal grains lack a number of nutrients which are essential for human health and well-being; additionally they contain numerous vitamins and minerals with low biological availability. Furthermore, the inability of humans to physiologically overcome cereal grain antinutrients (phytates, alkylresorcinols, protease inhibitors, lectins, etc.) is indicative of the evolutionary novelty of this food for our species. This genetic maladaptation between human nutrient requirements and those nutrients found in cereal grains manifests itself as

vitamin and mineral deficiencies and other nutritionally related disorders, particularly when cereal grains are consumed in excessive quantity. More disturbing is the ability of cereal grain proteins (protease inhibitors, lectins, opioids and storage peptides) to interact with and alter human physiology. These interactions likely occur because of physiological similarities (resultant from phylogenetic commonalities) shared between humans and many herbivores which have traditionally preyed upon the gramineae family. The secondary compounds (antinutrients) occurring in cereal grains (gramineae family), were shaped by eons of selective pressure and were designed to prevent predation from traditional predators (insects, birds and ungulates) of this family of plants. Because primates and hominids evolved in the tropical forest, wherein dicotyledonous plants prevailed, the human physiology has virtually no evolutionary experience with monocotyledonous cereal grains, and hence very little adaptive response to a food group which now represents the staple food for many of the world's peoples.

Cereal grains obviously can be included in moderate amounts in the diets of most people without any noticeable, deleterious health e ects, and herein lies their strength. When combined with a variety of both animal- and plant-based foods, they provide a cheap and plentiful caloric source, capable of sustaining and promoting human life. The ecologic, energetic e ciency wrought by the widespread cultivation and domestication of cereal grains allowed for the dramatic expansion of worldwide human populations, which in turn, ultimately led to humanity's enormous cultural and technological accomplishments. The downside of cereal grain consumption is their ability to disrupt health and well being in virtually all people when consumed in excessive quantity. This information has only been empirically known since the discovery of vitamins, minerals and certain antinutrients in the early part of this century.

The realization that cereal grain peptides interact with and induce change in human physiology and therefore elicit disease and dysfunction is even newer and dates to the early 1950s with the discovery of wheat gluten as the causative agent in celiac disease. In the past 10 years has come the evidence (admittedly incomplete) that certain cereal peptides may interact with the immune system to elicit a variety of autoimmune-related diseases. These two seemingly distinct entities (autoimmune disease and consumption of a staple food) are connected primarily through an evolutionary collision of dissimilar genes which bear identical products (molecular mimicry). Although, cereal grain consumption may appear to be historically remote, it is biologically recent; consequently the human immune, digestive and endocrine systems have not yet fully adapted to a food group which provides 56% of humanity's food energy and 50% of its protein.

Cereal grains are truly humanity's double-edged sword. For without them, our species would likely have never evolved the complex cultural and technological innovations which allowed our departure from the hunter-gatherer niche. However, because of the dissonance between human evolutionary nutritional requirements and the nutrient content of these domesticated grasses, many of the world's people su er disease and dysfunction directly attributable to the consumption of these foods.

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